STUDIES ON TRICHINOSIS, WITH ESPECIAL REFERENCE TO THE INCREASE OF THE EOSINOPHILIC CELLS IN THE BLOOD AND MUSCLE, THE ORIGIN OF THESE CELLS AND THEIR DIAGNOSTIC IMPORTANCE

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PLATES XXV-XXVII.

INTRODUCTION.

Since the discovery by Zenker of the Trichina spiralis as a lethal agent in the human being, and the placing of the disease trichinosis or trichiniasis on a firm clinical basis, the subject has been studied with great care from many points of view. Indeed, the fact that with the study of this affection—its ætiology, symptomatology, pathology and prophylaxis—such names as those of Virchow (70), Leuckart (40), Cohnheim (13) and Zenker (74) are intimately connected, vouches for the completeness of our knowledge regarding many of its features.

Modern methods, however, have given rise to new possibilities in the line of more minute histological and pathological study, and it is to this fact and to the unusually favorable conditions surrounding the present cases that this contribution owes its origin.

The Trichina spiralis was discovered in the human cadaver in 1835 by Owen (53); it possessed, however, mainly zoological interest until, by the work of Zenker in 1860, a strong stimulus was given to the study of the trichina and of trichinosis. The various German epidemics (13, 57, 42) occurring since then have furnished abundant material for investigators, and as a result of their observations and experiments it is now known that the main source of infection in man is incompletely cooked pork, which in a certain percentage of instances contains encapsulated trichinæ in the muscle fibres.

After trichinotic flesh has been eaten the capsules are dissolved off by the gastric juice; the worms pass into the small intestine, where

they reach their sexual maturity; copulation then takes place, and on the 6th or 7th day after the ingestion of the meat the first embryos appear. From the intestine the embryos pass to the muscular tissues. Some, especially Leuckart (40), regard this passage as taking place by an active boring of the embryos through the loose connective tissue; others (14, 2, 21) think that the distribution occurs chiefly through the vascular and lymphatic systems, a view which the recent work of Cerfontaine (14) and Askanazy (2) seems to favor. These observers assert that the female worms, after penetrating the villi, bring forth their young directly in the lymph spaces. After the embryos have reached the muscles, changes take place in them which will be described a little later.

CLINICAL HISTORY OF CASE I.

In the following case which was under observation in the medical clinic of the Johns Hopkins Hospital from March 3 until May 13, 1896, the blood was examined daily, with a determination of the number of leucocytes per cubic millimetre and a differential count of the various forms; frequent examinations of the urine and quantitative determinations of the uric acid, urea and total nitrogen were made, while on two different occasions small pieces of muscle were removed and subjected to careful microscopic examination.

Robert T., aged 23 years, an Englishman by birth, was admitted to the hospital on March 3, complaining of general pains. His past history was of no especial interest excepting that for the last three months he had been living the life of a tramp, with continual exposure to the weather and with insufficient nourishment.

Six weeks before entering the hospital he began to complain of general pains, as he expressed it, in the joints, bones and muscles. For the last two weeks he had been much worse, scarcely able to move about. On entrance he complained of a feeling of fulness in his head. No diarrhœa; no cough; no œdema at any time.

Physical examination showed the patient to be rather pale; tongue thickly coated; the temperature at time of admission was 102° F.; pulse 104; respirations 24. Examination of the thorax was negative, except for a soft systolic murmur heard all over the cardiac area; very faintly heard in the mid-axilla. Patient complained of general soreness in the limbs. Pressure on the muscles almost everywhere caused great pain, particularly in the right biceps. There was no tenderness apparent in the bones or in the skin. Spleen not palpable; no rose spots. Urine:

color normal; acid; 1028; albumin, trace; sediment, slight, showing mucous cylindroids, hyaline and granular casts. Diazo-reaction was not present.

Examination of the blood on March 5 showed 17,000 leucocytes with 37 per cent of eosinophiles. The absence of rose spots and of any palpable enlargement of the spleen, as well as the presence of a leucocytosis and the extraordinary increase in eosinophilic cells, rendered the diagnosis of typhoid fever, which was at first considered, improbable. The extreme muscular tenderness on pressure and on voluntary or passive motion, and the irregular temperature, suggested rather a myositis, and a diagnosis of trichinosis was made.

On further questioning the patient stated that six or seven weeks previously he began to have vague pains and heavy feelings in the muscles of his legs, and that he had repeatedly eaten raw or incompletely cooked pork during this period.

To confirm the diagnosis, on March 12 a small piece of muscle was removed under cocaine from the right biceps, where the pain was greatest at that time. A teased specimen of this showed, on microscopic examination, trichinæ, the majority actively motile, a few apparently non-motile; none were encapsulated, but many were surrounded by a finely granular material. During the remainder of the patient's stay in the hospital the symptoms gradually abated; the temperature, which had run a very irregular course, slowly descended to the normal point, and the sensitiveness of the muscles to pressure decreased. Œdema of the ankles appeared on two occasions in April after walking about the ward for several days, but both times quickly disappeared after rest in bed.

On May 13 the patient was discharged, the following note being made: "For from two to three weeks there has been no pain in the muscles; the stiffness has wholly disappeared and the patient feels perfectly well in every way, excepting that violent exertion is not readily borne."

Thus it will be seen that in many respects our case showed the classical picture of trichinosis. The pain in the muscles, aggravated by pressure or motion, the similarity of the early symptoms to those of typhoid fever, the œdema of the ankles after exercise, and the rather irregular fever, were characteristic. The absence of any history of gastro-intestinal symptoms, usually so marked, was probably due partly to the fact that this was not a case of extreme severity and partly to the incoherence of the patient on admission.

THE BLOOD.

Although it was known to the older pathologists that there were various kinds of white cells in the blood, it is only since the demonstration by Ehrlich (19) of their varied reactions to different dyes that we have possessed an adequate means of differentiating the various forms and of studying their relative proportions, one to another, in health and disease.

Morphologically, and by means of these tinctorial reactions, the leucocytes may, as is well known, be divided into five classes:

(1) Small mononuclear cells.
(2) Large mononuclear cells.
(3) Transitional cells.
(4) Polymorphonuclear neutrophilic cells.
(5) Eosinophilic cells.

In the first two divisions—the small and large mononuclear cells (the classification being determined by the fact that they are smaller or larger, respectively, than the ordinary polymorphonuclear neutrophiles) —the protoplasm shows no evidence of specific granulation and the nucleus is round or oval.

In the cells of the third division—the transitional—the nucleus becomes notched or indented and the protoplasm shows sometimes a slight tendency to neutrophilic granulation.

In the last two varieties, the polymorphonuclear neutrophiles and the eosinophiles, the granulations are well marked, in the former being fine and neutrophilic, in the latter coarse, highly refractive and acidophilic. The nucleus of the former is polymorphous; of the latter usually also polymorphous, although sometimes round or oval.

Many of the English school, notably Kanthack and Hardy (36), and Gulland (24), regard the so-called neutrophilic granulations as slightly acidophilic, and for this reason call the cells containing them the finely granular oxyphiles or acidophiles or eosinophiles. In the present work, however, the name polymorphonuclear neutrophiles (or cells with the ε granulation) will be used in describing them.

The percentage of these various forms in the blood differs quite markedly within normal limits. The usual proportions in the adult as given by Kanthack are:

Small mononuclears	15-25 per cent.
Large mononuclears and transitional forms	6 "
Polymorphonuclear neutrophiles	70-75 "
Eosinophiles	1-5 "

Concerning the proportion of the cells about which we are especially interested, the eosinophiles, various observers have given slightly different figures; Ehrlich (19*c*) regards it as from 2-4 per cent usually, although sometimes normally reaching 10 per cent; Hayem (31) as 7 per cent; Gabritschewsky (25), 1-3 per cent; Müller and Rieder (47*b*), 1-4 per cent; Canon (15), 1-3 per cent; v. Limbeck (41), 2-8 per cent; Uskov (quoted in 58), 6 per cent; Zappert (73), 0.67-11 per cent; while Weichselbaum (64) and Gollasch (26) each gives 5 per cent, including the transitional forms.

In this study the average number of leucocytes per cmm. has been taken to be 6500, of which 74 per cent (4810) should be polymorphonuclear neutrophiles, 18 per cent (1170) small mononuclears, 6 per cent (390) large mononuclears and transitionals, 2 per cent (130) eosinophiles.

Ever since the discovery of the specific cell granulations the eosinophilic cells have attracted the attention of many investigators who have studied the changes in the blood, especially in reference to the increase or decrease of this particular form in various pathological conditions. Much greater diagnostic significance than would seem to be warranted has, in many instances, been ascribed to this increase or decrease. Nevertheless, in certain diseases, chief among which are bronchial asthma and spleno-myelogenous leukæmia, a constant increase in these cells has been noted.

In the latter disease, as noted by Schwarze (60), Spilling (61), and Müller and Rieder (47*b*), the increase is more absolute than relative, owing to the enormous increase in the total number of leucocytes per cmm. In bronchial asthma an increase, both relative and absolute, has been described by Gollasch (26), Fink (20) and Gabritschewsky (25). In certain affections of the skin, especially pemphigus, prurigo, psoriasis and chronic eczema, a marked increase in eosinophiles has been noted by Canon (15) and Neusser (51). Kotschetkoff (37) describes an increase in scarlet fever, and Zappert (73) and Müller and Rieder (47*b*) in anchylostomiasis. Besides these, many isolated reports of an increase are to be found, although in many cases this has been too slight to be of significance. An increased percentage of eosinophiles has been noted in syphilis (4), malaria (1, 17, 27*a*), diseases of the genital organs and bones (51), mental diseases (51), during childhood (29), and after the injection of tuberculin (27*b*, 69, 5).

The largest percentages of eosinophiles hitherto reported have been 22.40 per cent in bronchial asthma (25), 33.02 per cent and 29.28 per cent in two cases of pemphigus, 27.9 per cent in anchylostomiasis (73), and 21.1 per cent in anterior poliomyelitis (47*b*). In a case of chronic eczema attending the Johns Hopkins Hospital, three different counts of the blood gave 22.6, 24 and 22.6 per cent of eosinophiles.

In the present case an examination of the blood on March 5 showed that the eosinophiles constituted 37 per cent of all the leucocytes—so striking an increase above the normal that from that time until the patient's discharge the blood was examined daily, and a determination of the number of leucocytes per cubic millimetre and a differential count of the various forms were made.

As a routine proceeding in making the differential estimate 500 leucocytes were counted daily, the stain employed being Ehrlich's triple stain (orange G., acid fuchsin and methylene green). In the case of the larger percentages an additional 500 stained in a different mixture (hæmatoxylin and eosin, methylene blue and eosin, Chenzinsky's solution, Huber's or Weichselbaum's modification of Ehrlich's triacid stain, Neusser's modification of the triple stain) were counted as a control.

The cover-glass preparations from which these counts were made were fixed either by Ehrlich's method of heating at 110° C. for from 1 to 1½ hours, or by Nikiforov's method of immersion in a mixture of equal parts of absolute alcohol and ether for two hours. The Zeiss mechanical stage was employed in studying the preparations.

In determining the number of leucocytes per cubic millimetre the Thoma-Zeiss hæmocytometer was used, the diluting agent being either Toison's mixture or an ⅓ per cent solution of acetic acid.

The red blood corpuscles, counted at various intervals during the disease, showed a gradual increase from 4,200,000 per cubic millimetre, three days after the patient's admission, to 4,900,000 per cubic millimetre on the day of his discharge.

When we consider the changes which the blood underwent during the two months of the patient's stay (see Table I, p. 322, and the Chart (Plate XXV)), some very interesting facts are brought out.

From their original percentage of 37, the eosinophiles gradually fell to between 10 and 15 per cent, where they remained for about two weeks, the number of leucocytes per cubic millimetre during this period ranging between 15,000 and 20,000. On March 26 the percentage of eosinophiles began to rise, this rise continuing steadily and gradually until April 23, when it reached 68.2 per cent; this means that *more than two-thirds of all the white blood cells were eosinophiles.* During this time an absolute increase in the leucocytes was also noted, the number per cubic millimetre averaging 27,500 between April 8 and April 22. From April 23 the percentage of eosinophiles decreased, and there was also a decrease in the total number of leucocytes, and on May 12, the day previous to the patient's discharge, 16.8 per cent and 11,000 were found respectively.

During the whole time the character of the eosinophiles was apparently perfectly normal—their nuclei were almost exclusively polymorphous, and they were slightly larger than the polymorphonuclear neutrophiles (Plate XXVI). As was to be expected, the percentage of these latter (always quite normal in character) varied inversely with that of the eosinophiles, reaching as high as 80.4 per cent and sinking as low as 6.6 per cent. The striking nature of this inverse relationship may be better appreciated if one studies the accompanying table and the chart (Plate XXV).

The small mononuclear leucocytes, scanty at first, soon increased to between 10 and 20 per cent, where they subsequently remained; in fact the percentage of both small and large mononuclear and transitional forms showed very slight fluctuations.

It is interesting to note that after about two weeks the percentage of small mononuclears kept fairly constant, being about that normally found in the blood. When we consider the very marked leucocytosis, this indicates that the total number of small mononuclears was much increased. When and how this increase takes place, however, must be left open to conjecture.

A few typical myelocytes were seen, averaging less than 0.3 per cent, probably no more than one would expect with so marked a leucocytosis.

TABLE I. CASE I.—SHOWING TOTAL NUMBER AND PERCENTAGE OF VARIOUS KINDS OF LEUCOCYTES.

Date.	Leucocytes per cmm.	Percentage of Various Forms of Leucocytes.				Number of the Various Forms per cmm.			
		P. M. Neut.	S. Monos.	L. M. and T.	Eos.	P. M. Neut.	S. Monos.	L. M. and T.	Eos.
March 5....	17000	55.0	3.0	5.0	37.0	9350	510	850	6300
6....	16500	50.0	5.0	7.0	38.0	8250	825	1120	6120
7....	17500	53.0	3.0	7.4	36.4	9275	525	1200	6300
8....	25300	60.9	1.9	5.9	31.4	15000	500	1500	7750
9....	22300	70.8	2.0	4.5	22.7	15300	440	900	5060
10....	16500	74.7	3.1	8.0	15.1	12000	480	1280	2400
11....	21167	75.1	2.8	2.4	18.6	15800	630	500	3700
12....	17500	77.8	4.4	3.0	15.1	13600	770	510	2625
13....	18833	77.6	2.1	3.7	16.6	13860	380	710	3000
14....	13800	74.6	4.3	4.0	14.9	10300	580	560	2100
15....	13750	74.0	7.6	3.2	13.6	10300	1000	420	1720
16....	13250	78.7	5.3	2.1	13.8	10400	680	270	1700
17....	16000	73.2	11.3	1.9	13.5	11700	1770	310	2160
18....	17750	77.4	10.9	1.7	10.0	13800	1970	300	1775
19....	20400	71.1	13.1	2.3	13.1	14200	2600	460	2600
20....	15700	76.5	10.1	2.2	11.2	12100	1570	340	1760
21....	16800	72.9	13.2	1.8	12.1	12400	1210	320	2040
22....	14000	79.2	10.8	1.7	8.3	11200	1540	240	1130
23....	16800	73.6	10.4	1.6	13.5	12400	1700	270	2200
24....	19600	74.6	11.2	1.8	11.2	14800	2200	360	2200
25....	17600	80.4	8.9	1.6	8.7	14400	1600	290	1560
26....	24000	69.2	12.7	2.0	15.4	16800	3120	480	3700
27....	20300	69.9	11.2	2.2	16.0	14000	2240	440	3200
28....	24100	68.3	10.1	2.4	18.9	16300	2400	580	4560
29....	20700	69.4	5.7	1.4	22.9	14000	1180	300	4600

TABLE I.—*Continued.*

Date.	Leucocytes per cmm.	Percentage of Various Forms of Leucocytes.				Number of the Various Forms per cmm.			
		P. M. Neut.	S. Monos.	L. M. and T.	Eos.	P. M. Neut.	S. Monos.	L. M. and T.	Eos.
March 30....	22300	60.7	9.6	3.0	26.0	13400	2200	670	5720
31....	22200	57.4	11.2	3.2	27.8	12600	2500	680	6160
April 1....	24300	60.7	7.9	3.4	27.8	14400	1920	840	6720
2....	23800	59.3	11.6	3.0	25.0	14100	2760	710	5950
3....	25200	53.3	13.3	2.8	30.0	13300	3300	700	7500
4....	23400	49.9	13.3	3.0	32.8	11700	3200	710	7590
5....	24300	48.8	13.2	4.0	33.8	10100	3150	960	7160
6....	24700	51.2	14.0	3.6	31.6	12700	3500	650	7900
7....	25100	48.4	14.5	2.5	33.7	12100	3600	625	8600
8....	29600	45.2	11.6	4.0	38.8	13500	3450	1180	11600
9....	28900	45.0	13.3	3.2	38.3	13000	3850	930	11000
10....	24500	45.8	12.2	3.8	38.0	11300	3100	900	9300
11....	29800	42.2	14.0	4.0	39.8	12600	4150	1180	11900
12....	28000	44.0	14.8	2.5	38.7	12300	4150	700	10800
13....	24200	42.0	11.8	1.4	44.2	10000	2880	340	10700
14....	33300	38.6	13.2	3.8	44.0	12800	4400	1300	14700
15....	28100	34.8	19.6	1.6	44.0	8600	5550	450	12300
16....	25400	30.4	16.8	3.0	49.6	7600	4200	750	12400
17....	27000	31.8	13.2	3.4	51.2	8600	3500	920	13700
18....	35700	27.2	14.4	3.8	54.6	9700	5140	360	19500
19....	29000	26.6	12.0	3.6	58.2	7700	3480	1040	16900
20....	19200	22.2	12.4	4.2	61.0	4200	2350	800	11600
21....	23000	16.6	16.0	3.8	63.6	3800	3680	870	14600
22....	26600	10.4	18.8	7.4	63.4	2700	4900	1950	16500
23....	17700	6.6	19.6	5.2	68.2	1170	3400	880	11070

TABLE I.—*Continued.*

Date.	Leucocytes per cmm.	Percentage of Various Forms of Leucocytes.				Number of the Various Forms per cmm.			
		P. M. Neut.	S. Monos.	L. M. and T.	Eos.	P. M. Neut.	S. Monos.	L. M. and T.	Eos.
April 24....	18800	7.2	23.4	4.4	64.8	1370	4400	840	12200
25....	15600	8.8	19.2	7.2	64.8	1370	2990	1020	10400
26....	17000	12.4	14.2	6.0	67.4	2100	2410	1020	11400
27....	12000	20.0	8.6	7.4	64.0	2400	1030	890	7700
28....	11100	18.2	17.6	7.2	57.0	2020	1950	800	6330
29....	12800	19.4	19.4	6.8	54.4	2470	2480	870	6990
30....	13200	20.8	17.2	8.2	53.8	2750	2270	1080	7020
May 1....	11000	21.8	16.0	12.0	50.2	2400	1760	1320	5520
2....	8900	27.4	17.8	8.4	46.4	2440	1580	740	5160
3....	10700	36.8	15.0	6.8	41.4	3940	1600	710	4430
4....	10700	34.8	20.8	6.4	38.0	3720	2120	680	4070
5....	11000	45.6	19.0	6.6	28.6	5020	2090	710	3150
6...	10300	41.0	20.2	4.8	33.6	4220	2080	490	3460
7....	12300	50.8	20.2	6.0	23.0	6250	2480	740	2830
8....	11500	54.0	18.0	4.0	24.0	6210	2070	460	2760
9....	11500	59.8	17.6	6.2	16.4	6850	2020	710	1890
10....	15700	51.0	12.8	5.6	20.4	7990	2010	880	3200
11....	13500	62.4	14.2	4.8	18.8	8420	1920	650	3540
12....	11000	64.0	14.4	4.8	16.8	7040	1580	530	1850

If one estimate the total number of these various forms per cubic millimetre (see Table I, p. 322) by multiplying the percentage of the individual variety by the total number of leucocytes per cmm., it will be found that, for a period of two weeks, the polymorphonuclear neutrophiles were *absolutely decreased* in amount—a very striking fact when one considers the marked leucocytosis. This tends to show even more clearly the remarkable relationship which exists between the neutrophiles and the eosinophiles, the latter cells being greatly increased in number during the same period.

Plate XXVI shows a typical microscopic field of the blood of Case I. The three most striking points furnished by the study of the blood are:

(1) The remarkable increase in the number of the eosinophiles, which amounted to 68.2 per cent of all the leucocytes present, 35 per cent more than has ever hitherto been reported.

(2) The coincident diminution in the number of the neutrophiles, these cells and the eosinophiles being at all times in inverse proportion.

(3) The marked leucocytosis.

The presence of such great quantities of eosinophiles in the blood in this case is a point of especial interest. If further observation shows this change to be characteristic we shall be furnished with a symptom of the greatest diagnostic value in this disease, and one which, perhaps, may help to clear up some of the cases which are regarded *intra vitam* as rheumatic in nature, the true diagnosis being revealed only years afterwards upon the autopsy table.

As an association has for a long time been noted between the eosinophiles and the Charcot-Leyden crystals, occurring so commonly in the spleen and marrow in leukæmia (52*b*) and in the sputum in bronchial asthma (20, 45, 46, 54), it was regarded as interesting to see whether from the blood in this case, containing as it did such large quantities of eosinophiles, the crystals might be obtained.

For this purpose blood was withdrawn on nine occasions, placed sometimes in sterilized, at other times in unsterilized vessels, some kept in the thermostat at 37.5° C., others at room temperature; but,

although repeated and careful microscopical examinations were made at frequent intervals during a period of several weeks, in none of the specimens were any Charcot-Leyden crystals to be found.

This completely harmonizes with the conclusions reached by H. F. Müller (47*a*), who carried on investigations of a like nature upon the contents of fresh pemphigus vesicles, which also contain great quantities of eosinophilic cells. Thus it seems highly probable that the Charcot-Leyden crystals are, at least, not *direct* crystallization products of the eosinophiles and that something besides the presence of these cells is necessary for their formation.

THE URINE.

The urine, as has been mentioned, showed a trace of albumin, hyaline and finely granular casts and a small number of pus cells. No sugar was found. Ehrlich's diazo-reaction was never present.

A systematic quantitative study of the nitrogenous elements of the urine was carried on chiefly in connection with the ideas of Horbaczewski (30). This observer, as is well known, believes that the uric acid excreted by the animal organism is derived from the destruction of nuclein-holding material and mainly from the destruction of leucocytes.

This view is based on the following assumptions:

(1) That outside the body we may obtain uric acid from nuclein-holding substances.

(2) That in leukæmia and leucocytosis, where there is a greater destruction of leucocytes, there is a distinct increase in the uric acid excretion.

(3) That in many pathological conditions where nuclein-holding substances are destroyed, as in fevers, conditions of inanition, phosphorus-poisoning and cachexia, the increase in uric acid is also noted.

(4) That in the experimental leucopenias, produced by quinine and atropine, a diminution in the uric acid excretion may be shown.

The quantitative work was carried on in this case mainly with a view to control the second of the above statements, that is that a parallelism exists between the extent of the leucocytosis and the

amount of uric acid excreted, a parallelism which has, however, been denied by Mareš (48), who regards the uric acid as a by-product in leucocyte formation.

To determine this question in the present case the total quantity of uric acid excreted during the 24 hours was determined on 23 different occasions; on four of these days the total nitrogen and on four others the total urea per 24 hours was also estimated.

The uric acid was determined by the Hopkins method—precipitation of the uric acid from 100 cc. of the urine by saturation with ammonium chloride, filtration, solution of the uric acid, reprecipitation with strong hydrochloric acid and final titration with potassium permanganate. The total nitrogen was estimated by the Kjeldahl method, *i. e.* conversion of all the nitrogen into ammonia and titration with a standard solution of oxalic acid. The urea was determined by oxidation with sodium hypobromite, and measurement of the nitrogen given off.

TABLE II. CASE I.—URINE CHART.

Date.	Total Quantity per 24 Hours of			Ratio of	
	Uric Acid.	Urea.	Total Nitrogen.	Uric Acid : Urea.	Nitrogen in Uric Acid : Total Nitrogen.
March 15....	.2423 gram.				
16....	.2092 "				
17....	.5722 "				
18....	.7800 "				
19....	.8180 "				
20....	.3869 "				
21....	.4053 "				
22....	.2088 "				
23....	.7935 "				
24....	.3119 "				
25....	.4579 "				
26....	.4542 "				
27....	.1975 "				
28....	.5882 "				
April 3....	.3685 "		7.9497 grams.		1 : 64.7
4....	.2829 "		7.2300 "		1 : 76.6
5....	.2753 "		4.6725 "		1 : 50.9
6....	.3619 "		4.8027 "		1 : 39.8
7....	.3971 "				
24....	.2905 "	10.79 grams.		1 : 37.1	
28....	.3716 "	19.22 "		1 : 51.7	
29....	.4893 "	29.11 "		1 : 59.4	
30....	.2946 "	17.21 "		1 : 58.4	

By examination of Table II it will be seen that on no occasion did the total uric acid excretion, the ratio of uric acid to urea excretion, or the ratio of nitrogen in the uric acid to the total nitrogen in the urine, rise to any extent above the limits usually regarded as normal.

The normal quantity of uric acid and the normal ratio of this to the urea is given somewhat differently by different authors; by Hammarsten (32) as 0.7 gramme and 1:50-70; by Halliburton (33), 0.55 gramme and 1:60; by Vierordt (71), 0.67 gramme and 1:45; and by v. Jaksch (35), 0.21 gramme and 1:60 respectively. Hammarsten (32) gives the normal ratio of nitrogen excreted in the form of uric acid to the total nitrogen as 1:69.3.

Thus the results obtained in this case show such a slight, if in fact any, relative or absolute increase in the uric acid excretion that they speak against the views of Horbaczewski; for if this author's results are universally correct we should expect a decided increase—absolute or at least relative—in the uric acid excretion in a case where the leucocytes were as markedly increased as they were in our case. It is an interesting fact, however, that here the eosinophiles and not the neutrophiles, as is usually the case in a marked leucocytosis, were the elements especially increased.

THE MUSCLES.

The changes in the muscles in trichinosis have, of course, been repeatedly and carefully studied; in the early sixties by Virchow (70), Zenker (74), Fiedler (21), Cohnheim (13) and many others; more recently by Soudakewitch (62), Lewin (43), Geisse (28) and Finger (22). All of these observers describe the presence of the parasites in the primitive muscle bundles and the granular degeneration which takes place about them; they further speak of the great proliferation of the muscle nuclei, so that in some places, especially in the region of the invaded fibre, there may be great masses or clumps of nuclei situated in undifferentiated sarcoplasm. In other places swelling and degeneration of the nuclei have been described. The method of formation of the capsule or cyst wall which surrounds the parasite after it has been in the muscle a certain length of time is still undecided. Many ideas have been held. It has been suggested that it arises from a thickening of the sarcolemma (70*a*, *b*, *d*, 6); from the interfascicular connective tissue (16); from the finely granular degenerative detritus (74*a*); or partly

from secretion from the worm itself and partly from inflammatory changes in the surrounding connective tissue (7). The more modern observers have described further changes not mentioned by the older pathologists.

Finger (22) notes the presence of great numbers of small round cells about the vessels and capsules and in the interfibrillar connective tissue, and the splitting up of the contents of the sarcolemma sheaths into small irregular bits, in most of which the cross striation has been lost.

Soudakewitch (62), besides this breaking up of the muscle fibre into little bits, notes also the presence of great numbers of leucocytes which he regards as phagocytes of the degenerated fibres. This phagocytic action is also shared by elements which he regards as muscle-cells, and which arise by the separation from the rest of the muscle fibre of the nucleus with some of the muscle substance about it. These structures appear to maintain for a while an independent existence, but soon undergo destruction.

Lewin (43) has devoted himself more especially to the cell changes. He describes the proliferation and great hypertrophy of the muscle nuclei in the fibres containing trichinæ, with a degeneration of many of these nuclei as shown by the affinity of the nucleoli for the acid stain; the splitting up of the muscle fibre into separate cells; the formation of separate cells of the kind regarded by Soudakewitch as phagocytic muscle cells, and the local œdema of many of the fibres.

The portions of muscle removed in this case, both of which came from the right biceps, were hardened immediately, the specimen of March 12 in alcohol, that taken two weeks later in bichloride of mercury. On microscopic examination many of the above described changes are to be noted (Plate XXVII).

In the first specimen the reaction is especially marked in a few foci; in some places the fibre containing the parasite has become converted into a finely granular, faintly staining material, containing many large, swollen nuclei—the proliferated muscle nuclei—the nucleoli here taking the usual deep blue hæmatoxylin stain. The sarcolemma shows slight thickening, but there is no very marked heaping up of cells outside of it except in a very few places. Elsewhere absolutely no change in the muscle fibre is to be seen, excepting a small layer not thicker than the diameter of a red blood corpuscle, surrounding the parasite, which is very small; in fact, the whole picture points conclusively to a very recent infection.

In many of the fibres not containing parasites marked nuclear proliferation is seen; in some this is found in conjunction with granular degeneration of the muscle substance, in others with no apparent changes; about the nuclei, especially of the former, a distinct but rather small vacuole may be made out, a sign, probably, of lowered vitality of the nucleus.

A peculiar fragmentation of the muscle is sometimes to be noted. At times it takes place in the direction of the long axis of the fibres, which break up into separate fibrillæ or bunches of fibrillæ; at other times it occurs in an irregular manner. In a few places a peculiarly interesting picture is observed, the fragmentation being transverse and the axis of the proliferated nuclei running also in a transverse direction, thus splitting the muscle into distinct disks. Whether in this latter mode of fragmentation the division had occurred at the membrane of Krause or the plane of Hensen could not be made out, owing to the obscuring of the field by the great number of proliferated muscle nuclei.

Throughout the specimens there are to be seen cells whose protoplasm shows a marked affinity for the eosin stain. These cells contain one nucleus or sometimes two or three, generally of rather large size. The fact that some of these elements are still in part connected with the muscle fibre, and that in the protoplasm of some there are still evidences of striation, points at once to their origin by the separation of a certain amount of muscle substance, containing one or several nuclei from the primitive muscle bundle.

These cells, together with bits of degenerating muscle, some pale and granular, others taking on a deep eosin stain, but both showing a total or almost complete loss of striation, and many pale and swollen muscle nuclei, are seen in quite large numbers in certain scattered foci of degeneration present in the muscle.

What is of especial interest, however, is that all through the muscle, between and within the fibres, but especially in those areas made up largely of cells and debris, many polymorphonuclear cells are seen; some of these are ordinary pus cells, neutrophiles; others show large red refractive acidophilic granules in the cell body, *i. e.* they are

eosinophiles; in some again the protoplasm, though finely granular, shows a distinct affinity for the eosin stain; in other words, the character of the cells appears to be half-way between that of the neutrophiles and that of the eosinophiles.

These cells would appear to be phagocytic in nature, for they are especially abundant in the more degenerated areas, and in many places are seen in little bays or inlets or lakes in the degenerating muscle, as if gnawing it away. It was thought at first that perhaps these cells might ingest bodily the little rod-shaped bits or fragments which are found especially at the ends of the degenerating muscle fibres and which with the hæmatoxylin and eosin stain show considerable resemblance to the granules in the eosinophilic cells; but staining with other double stains and with the triple stain showed that this supposition is hardly tenable, since the staining properties of the two are markedly different. The degenerated substance if taken up by the leucocytes must undergo a rapid disintegration within the cell body or possibly may be taken up in a soluble form.

In the second specimen, taken two weeks later, more advanced stages of the same processes are seen. The trichinæ are larger, and in some cases two or three parasites are found in the same cyst; about the cysts there is a marked increase in the number of nuclei; in some cases true giant cells are formed, a number of nuclei lying in a mass of undifferentiated protoplasm, probably sarcoplasm, while throughout the whole specimen the nuclear proliferation is more marked. The transverse splitting of the fibres into disks and the transverse proliferation of the contained nuclei is more marked than in the preceding specimen, as well as the longitudinal and irregular breaking up of the fibres.

The vacuoles about the proliferating and degenerating nuclei are more marked; the muscle cells, mentioned above, show less affinity for the eosin stain and in some cases give evidence of granular degeneration; besides the slight thickening of the sarcolemma there is no distinct capsule about the parasites. Of the polymorphonuclear cells, the eosinophiles are much more common, the neutrophiles much less numerous; the former are present everywhere, but are found especially

in the scattered foci of more marked degeneration and about the ends of degenerating fibres (Plate XXVII).

That these were typical eosinophiles was shown not only by the character and size of their granules, but also by the fact that they showed the typical staining properties with acid fuchsin, orange G., picrate of ammonium and other acid stains, and the Biondi-Haidenhain triple stain for tissues as well as with the ordinary hæmatoxylin and eosin stain (Plate XXVII).

In the interfibrillary connective tissue there was a slight proliferation of the cells, while the changes in the interfascicular connective tissue were barely evident. In the blood-vessels in the latter, counts of the white blood cells showed that the neutrophiles and eosinophiles were present in about the same ratio (never differing more than 3 or 4 per cent) as in the blood count of the corresponding day, thus suggesting that the eosinophiles were not attracted to the part to a greater extent than the neutrophiles.

The presence of such great numbers of eosinophiles was so striking that two specimens of trichinotic muscle, found in the Pathological Museum of the Johns Hopkins Hospital, were examined to see whether like changes were present.

In the first, a case of carcinoma mammæ in which trichinæ were found in the pectoral muscle, the capsules and parasites were for the most part calcified, although some showed fatty and fibrous change; in the muscle no especial changes were noted. This, of course, was a case of old standing, discovered by chance, probably years after the original infection.

The second specimen, fortunately, was from a case of acute trichinosis which had caused the death of the patient, a New York butcher, six weeks after the onset of the disease. Here the muscle is studded with cysts, each containing from one to six trichinæ, while about these, and in fact all through the muscle, great quantities of nuclei are seen, about many of which there are distinct vacuoles; in some cases the nucleoli take the eosin stain. The muscle cells, mentioned before, here show still further degeneration; the protoplasm is granular and takes a yellowish color, while the nuclei stain very slightly with hæma-

toxylin. But what is most interesting is that here again numbers of typical eosinophiles are to be seen scattered everywhere throughout the specimen, but congregated more especially in the areas of more marked degeneration, side by side with the degenerating bits of muscle and the muscle cells.

Thus these two cases, both acute and both studied shortly after the infection, besides the marked changes in the muscles, characterized by the great proliferation of nuclei, the formation of muscle cells and their subsequent degeneration, the formation of distinct vacuoles about the proliferating and degenerating muscle nuclei, and the granular degeneration of many of the fibres, show an interesting and hitherto undescribed condition, namely, the presence of large numbers of eosinophilic cells. This fact, coupled with their coincident marked increase in the circulating blood, suggests one way at least in which these cells may arise in the body.

THE INCREASE IN THE EOSINOPHILIC CELLS.

Concerning the nature of the eosinophilic granules and the origin of the cells containing them, many widely divergent views have been held, some founded entirely upon staining reactions, others built on a somewhat firmer basis, all more or less hypothetical, some very far-fetched and bizarre.

Until the introduction of the Ehrlich stains, these coarse, refractive granules were regarded as fat droplets by Wharton Jones (34), who first described them in 1846, by Förster (23) and Biesiadecki (8), who saw them in the blood in leukæmia, and by Neumann (52), Bizzozero (9), Budge (10) and Mosler (49), who noted them in the bone-marrow in the same disease. The cells containing these granules are the coarsely granular leucocytes of Max Schultze (63).

The work of Ehrlich (19) and Schwarze (60) showed, however, that these large refractive granules are not fat droplets, but bodies possessing a chemical nature not clearly understood. Ehrlich first demonstrated the affinity of this granulation for the acid coloring matters. These eosinophilic granules, as they are now generally termed, are regarded by him and his school as a sort of nutritive reserve, built up by the cell for its own use or for excretion. Thus, according to Schwarze (60), they resemble somewhat the aleuron granules or crystalloids of plants

in being the products of a specific cell activity, and are probably not proteid in nature. Zappert (73) and Przewoski (56), however, insist that these granules are of the nature of proteid, the latter showing that their solubilities and chemical reactions correspond in many respects to this form of matter.

Many investigators, among whom may be mentioned Pouchet (55), Bannwarth (11) and Przewoski (56), basing their arguments upon the similarity in the reaction of these granules towards the acid aniline dyes, have regarded them as related to or identical with hæmoglobin, though Ehrlich (19) and Schwarze (60) deny this and show that there are quite marked tinctorial differences between the eosinophilic granules and hæmoglobin.

The demonstration of the presence of iron in these granules by Barker (12) is of especial interest in this connection.

Sherrington (65), who states that he demonstrated phosphorus in them by the Lilienfeld-Monti (44) method, regards them as a form of nucleo-albumin, while Kanthack and Hardy (36) consider them to be secretory products containing a zymogen, giving rise to alexines or other substances of great activity in phagocytosis and in conditions of inflammation and intoxication.

In all the above views the granules are regarded as paraplastic in nature. Gulland (24), on the other hand, holds that they are plasmatic; or, in other words, that they represent an altered condition of the microsomes and are connected by a mitoma.

As a consequence of this diversity of opinion regarding the nature of the granules, the mode of origin of the cells is still an unsolved problem. The view most generally held is that they are derived from the polymorphonuclear neutrophiles by a kind of ripening process, a view which was advanced by Max Schultze (63) and which is now held by Ehrlich (19), Gulland (24), Zappert (73) and many others. Müller and Rieder (47*b*, *c*) and van der Stricht (66) think that, besides this mode of formation, some eosinophiles are derived by mitosis from pre-existing cells of the same kind. Rénaut (59), Denys (18) and Arnold (3) describe amitotic division of these elements.

Max Schultze (63) and Müller and Rieder (47*b*, *c*) hold that this change takes place mainly in the circulating blood; according to Ehrlich (19) the bone-marrow is the only place where this transition occurs; while van der Stricht (66) and Zappert (73) think that blood and hæmatopoietic organs both play a part in this process.

Kanthack and Hardy (36) regard these elements as wandering cells whose home is normally the connective tissue; Saxer (68) thinks that all

leucocytes are derived from pre-existing primary wandering cells, while Gollasch (26), Neusser (51) and Weiss (72) believe that they are derived directly from the tissue elements.

Of those who think they can trace a relationship between eosinophiles and the red blood corpuscles, Przewoski (56) regards the eosinophiles as incompletely developed erythrocytes, *i. e.* derived from hæmatoblasts, while Sacharoff (67) believes that they are formed through the engulfing by leucocytes of nucleoli cast out by hæmatoblasts (nucleated red corpuscles) at the time when the latter are converted into erythrocytes.

The study of the blood and the tissues of our cases of trichinosis furnishes us with important evidence bearing upon the origin of the eosinophilic cells. The constant inverse relationship existing between eosinophiles and neutrophiles, the increase of the former being invariably coupled with a coincident decrease of the latter, so that the neutrophiles on some occasions were absolutely subnormal in number notwithstanding the marked leucocytosis, as well as the similarity in size and the character of the nuclei of the two varieties of cells, both point strongly toward some very close connection between the two forms. Indeed, the striking and constant inverse relationship between the neutrophiles and eosinophiles would appear to be strong evidence in favor of the view that the latter cells arise, in some instances at least, by direct transformation of the former. There is much also to suggest that this transformation may have occurred here in the muscles. The presence in the first piece of muscle of many neutrophiles, together with many typical eosinophiles and cells which might be regarded as transitional forms between the two, and the finding in the second specimen two weeks later of a greatly increased number of eosinophiles, harmonize with this idea, especially when we consider that *on both of these occasions the ratio of the neutrophiles to the eosinophiles in the peripheral blood and in the vessels of the interfascicular connective tissue was between four and five to one*, a very much larger ratio than that which exists between these cells in the muscle.

How such a transformation might take place one can only conjecture. One may imagine that the trichinæ on reaching the muscle act as a strong irritant or poison, giving rise to many tissue changes, and probably producing either primarily or secondarily chemotactic

substances which attract large numbers of leucocytes to the muscles, causing a marked leucocytosis, especially in the more degenerated portions. In these regions the polymorphonuclear neutrophiles wandering out of the vessels act as phagocytes upon the degenerating or degenerated bits of muscle. It is in these phagocytes apparently that the change in the character of the granules takes place.

By this it is not meant that the eosinophilic granules are bits of ingested material, but that they are elaborated by the cell itself. May not this result perhaps be due to the ingestion of some material originating from the degeneration of the muscle fibres, which may bring about some essential change in the character and chemismus of the cell?

Finally, we may well suppose that these cells wander or are swept back into the general circulation, giving us the marked increase in eosinophiles. Such a theory would not seem unreasonable, particularly when we consider the amount of muscle tissue in the body. The fact that practically no atypical neutrophiles or eosinophiles, *i. e.* evidences of transition, were seen in the blood itself speaks against the probability that such a change may have taken place in the circulation. Again, these small polymorphonuclear cells are certainly very different in appearance from the large, often mononuclear eosinophiles which we find in the blood and know to come from the marrow in leukæmia.

It is interesting to note that during the course of this investigation an article appeared by Kischensky (39), in which he comes to the same conclusion regarding the origin of the eosinophiles in the sputum of asthmatics, in which these cells are present in very large quantities, namely, that they are derived from neutrophiles.

After the completion of the above work and the publication of a preliminary note thereon in the *Johns Hopkins Hospital Bulletin* of April, 1897, a second case entered the Johns Hopkins Hospital, which in almost all respects tended to confirm the results obtained in the preceding investigations.

CLINICAL HISTORY OF CASE II.

The patient, E. B., a sailor, age 29, white, of German nationality, was admitted, April 15, 1897, complaining of fever, chills, muscular pains and weakness.

His past history shows that he has always enjoyed very good health; he gives no history of rheumatism nor of œdema, and has been only a moderate drinker. During his voyages his ship has often stopped at Cuba, but the sailors have never been allowed to go on shore, and he said there had been no sickness whatever amongst the crew. It was later found, however, that two members had malarial fever of the æstivo-autumnal type.

The present sickness dates from the first week in April. The onset was quite insidious; loss of appetite and general muscular weakness were noted, with occasional heavy painful sensations in the epigastrium. Headache set in for the first time on Friday, April 9, and continued until admission, the pain being especially marked in the frontal region. There had been considerable pain in the muscles of the back and especially in the calves of the legs since April 11. The bowels were regular until April 15, when the patient had two fluid stools, but no tenesmus. On April 10 the patient noticed a rather sudden œdema of the eyelids and face, causing him much discomfort and some pain in opening and closing the lids. He had had pain in the facial muscles during mastication for the last three days, while on deep inspiration there had been a slight pain through the chest. There had been no epistaxis. On board the ship the patient ate mostly salted meats and had frequently eaten raw sausage, though never raw ham. He had had shaking chills at times.

The physical examination showed heart and lungs negative; good color of lips and mucous membranes; gums normal; slight pain and stiffness in the masseters on opening and closing the mouth, and slight puffiness of the eyelids. Pressure on larynx is slightly painful, but no pain on pressure of calf muscles. No pain in arms and thighs. Spleen is just palpable; abdomen is a little full but not tender, and has upon it one or two spots somewhat suggestive of rose spots. There is no glandular enlargement; no tenderness or nodes on the long bones.

The temperature at first was of an intermittent type, rising each evening to between 103° and 105.5° F. and sinking to normal by the following morning. After April 24 the temperature continued normal until the time of the patient's discharge.

The stools, which continued to be of fluid consistence for some time, on frequent examinations showed no parasites or ova of parasites.

The urine was negative. The examination of the blood was made very frequently and carefully on many occasions, but no malarial parasites were ever obtained, nor were they obtained from the spleen, which was aspirated for this purpose.

The blood, however, showed other marked changes, chief among which was a great increase of the eosinophile cells, reaching 42.8 per cent on one occasion, accompanied by a moderate leucocytosis. This very marked eosinophilia, coupled with other points in the clinical history of the case, but mainly the eosinophilic increase, suggested the possibility that the case might be one of trichinosis. On April 28 a small piece of muscle from the calf was removed, and the diagnosis was confirmed by the demonstration in it of young non-encapsulated trichinæ. These were not present in such large numbers as in Case I, as might have been expected from the fact that the present patient complained of much less pain and in general showed less marked symptoms.

The subsequent history of the case was, as in the previous instance, a gradual cessation of all the symptoms, a disappearance of the muscular pain and a slow decrease in the percentage of eosinophiles, there being 17.6 per cent when he left the hospital, still a considerable increase above the normal.

THE BLOOD.

The blood in this case showed in many respects the same features as in the previous one (Table III). Both eosinophilia and leucocytosis, however, were less marked, as one would naturally have expected, since we were here dealing with a much less severe infection, if one may judge from the much milder clinical symptoms and the discovery of fewer parasites in the portion of muscle removed. As the patient was under observation a much shorter time, the table is not so complete as that belonging to Case I. The eosinophiles, which on admission made up 42.8 per cent of the total leucocytes of the blood, gradually sank to between 14 and 17 per cent, while in the corresponding period the polymorphonuclear neutrophiles rose from 43.1 to between 58 and 67 per cent (see Table III).

The leucocytosis varied between 6,000 and 13,000 during the patient's stay in the hospital, averaging about 10,000 and not varying markedly. The small mononuclears showed at first a tendency to be much decreased, as in the previous case; but, as was also seen before, showed later only slight fluctuations.

TABLE III. CASE II.—BLOOD CHART.

Date.	Leucocytes per cmm.	Percentage of the Various Forms of Leucocytes.				Total Number of Various Forms per cmm.			
		P. M. Neut.	L. M. and T.	S. Monos.	Eos.	P. M. Neut.	S. Monos.	L. M. and T.	Eos.
April 15....	13000	43.1	6.5	1.4	42.8	5600	180	840	5560
16....	....	47.7	4.7	4.5	39.1	....	....	....	....
17....	....	52.0	2.8	7.6	37.6	....	....	....	....
18....	8000	....	....	....	....	....	....	....	....
19....	....	57.2	2.8	8.0	32.0	....	....	....	....
20....	8900	55.2	3.8	11.2	31.8	4900	1000	340	2830
21....	8700	....	....	....	....	....	....	....	....
22....	10700	58.0	2.7	11.7	27.7	6200	1250	290	2960
23....	6000	56.2	2.0	15.2	26.2	3370	910	120	1570
24....	11000	60.4	4.0	13.2	22.4	6640	1450	440	2460
25....	11000	57.2	4.2	18.6	20.0	6290	2050	460	2200
26....	9600	60.7	5.3	12.3	21.7	5830	1180	510	2080
27....	11300	63.0	5.0	17.0	14.7	7120	1920	560	1660
28....	12700	62.7	4.0	17.0	16.3	7960	2160	510	2070
29....	12000	67.0	3.25	15.25	14.0	8040	1830	390	1680
May 1....	10700	58.3	4.0	22.0	15.7	6240	2350	430	1680
3....	13000	64.3	4.0	16.0	15.7	8360	2080	520	2040
5....	12000	64.7	4.0	16.0	15.3	7760	1920	480	1840
7....	9300	62.8	4.0	16.4	16.8	6140	1530	370	1560
10....	10700	60.4	2.8	16.4	20.0	6460	1750	300	2140
12....	11000	60.4	3.3	16.6	19.6	6640	1820	360	2160
14....	12000	58.8	2.8	18.8	19.6	7060	2260	340	2350
17....	9000	58.8	3.6	20.0	17.6	5290	1800	320	1580

When one considers the morphological structure of the different white blood cells one is again struck by the fact that mononuclear eosinophiles are almost entirely wanting, the nucleus of these cells being almost exclusively polymorphous and resembling in every way that of the neutrophiles. Here also, as in Case I, extremely few myelocytes were seen (averaging 0.03 per cent), and but few forms which could be regarded as transitional forms.

The number of red blood corpuscles per cmm. varied between 5,000,000 and 5,120,000.

THE MUSCLE.

The changes in the muscle in this case, although some of the features described before were lacking, resemble in many respects those seen in the first case. They were, however, by no means so well marked.

There is proliferation of the muscle nuclei, especially in the fibres, which show by their loss of staining properties a beginning degeneration. The number of degenerating fibres, however, is small, and these are entirely confined to the neighborhood of the trichinæ. The nuclei of the fibre containing the trichina are pale and greatly swollen, the nucleoli large and deeply staining; a few karyokinetic figures are seen.

Surrounding the large typically curved trichina in its muscle fibre, which shows granular degeneration, we have many small round cells, "muscle cells," muscle nuclei, polymorphonuclear cells (mostly neutrophilic, a few eosinophilic) and bits of muscles containing many swollen proliferated nuclei.

The striation of some of the degenerated fibres is entirely lacking; in others the peculiar granular degeneration noted in the first case is seen.

There are some eosinophiles scattered throughout the specimen, though not comparable in number to those noted in the first case; here more of the polymorphonuclear cells are neutrophiles.

There is no evidence of transition from neutrophiles to eosinophiles in this specimen. In fact the whole picture is one of a much less violent infection than in the first case. In all probability the trichinæ

had been in the muscle fibre a longer time than in the first case, since when the bit of muscle was removed the number of eosinophiles per cmm. had fallen to a comparatively low point, nor did they rise again, a point which suggested, as did the clinical history, that the infection had almost run its course.

Recently, since the preceding pages were placed in the hands of the editor, a third case of trichinosis has come under our observation, which tends still further to establish our belief in the conclusions arrived at from the study of the first two cases.

In this, as in the second case, the discovery of a largely increased number of eosinophiles in the peripheral circulation led to the idea that the case was one of trichinosis, and an examination of an excised bit of muscle again proved the correctness of this idea.

Case III.—The patient, J. Y., was admitted to the hospital, December 21, 1897, complaining of headache, pain in the side, chilly sensations and swelling of the feet. Six months previously he had been treated for typhoid fever in the hospital and still gave the Widal reaction. Seven years previously he had had an attack of acute articular rheumatism.

The patient lived with his German employer and frequently partook of sausages and other forms of swine meat, often insufficiently cooked.

For five weeks he had been feeling unwell, complaining of frontal headaches and coughing spells; there had been no herpes, nose-bleed nor shaking chills. Five days before entering the hospital the patient had had an acute attack of diarrhœa, having 5 to 8 thin, green stools daily, associated with severe griping pains in the abdomen. Two days after the commencement of the diarrhœa he had noticed that his legs, feet, hands and arms seemed numb and cold. The joints were stiff and the limbs swollen and his attention was called by his employer to his swollen eyelids.

On admission the physical examination showed an absence of rose spots, spleen not palpable, puffiness of the eyelids, great tenderness of the muscles of the arms and of the calf, with swelling of the former and a bluish mottling of the skin of the limbs.

The temperature reached 103° for the first few days and then gradually fell to normal; shortly after this the pain in the limbs and the intestinal symptoms decreased, and on January 16, 1898, the patient was discharged, apparently quite well except for slight soreness of the right leg.

The blood (Table IV) on admission showed 45 per cent of eosinophiles, and this, from the study of the two previous cases, led to the diagnosis of trichinosis and the subsequent confirmation of that diagnosis by the removal of a portion of muscle and the discovery of trichinæ therein.

TABLE IV. CASE III.—BLOOD CHART.

Date.	Number per cmm.		Percentage of			
	Red blood corpuscles.	Leucocytes.	Polymorphonuclear neutrophiles.	Large mononuclears and transitional.	Small mononuclears.	Eosinophiles.
Dec. 22..	....	....	48.4	4.7	1.5	45.4
23..	....	17,000	52.7	3.6	3.1	40.4
27..	4,700,000	15,300	42.4	4.0	5.6	45.0
Jan. 3..	4,300,000	12,000	42.2	4.2	4.6	49.0
7..	....	14,700	31.6	4.4	19.0	44.6
10..	4,546,000	....	32.4	3.0	21.8	42.8
14..	....	13,700	35.2	4.0	23.4	37.2
22..	....	9,000	45.5	2.0	17.7	34.7

During the stay of the patient in the hospital the proportion of eosinophiles varied very slightly, reaching 49 per cent on January 3 and sinking to 34.7 per cent on January 22. As in the other cases, the nuclei of practically all these cells were polymorphous; yet, as before, no forms were seen in the blood suggesting transitional stages between neutrophiles and eosinophiles. At first there was a smaller percentage than normal of the small mononuclears, which, however, increased later up to practically the normal, a condition which was noted in both the preceding cases. On one occasion, and only one, two typical myelocytes were seen. The leucocytosis was not marked, being 17,000 on December 23 and 9,000 on January 22 (see Table IV).

As in the preceding cases, it was impossible to determine how long the eosinophilia lasted, as in all three cases the patients left town and were lost from observation.

The stools, although examined repeatedly, showed no intestinal trichinæ.

The piece of muscle removed during the first week of the patient's presence in the hospital showed in almost all respects the same changes noted in the two previous cases, except in this case the specimens of the parasite found in the muscle were younger, smaller and less abundant than in the first case. In the muscle fibre in which the trichinæ were found there was a complete loss of striation and a tendency to take on a faint bluish stain. In these fibres the proliferated and greatly swollen muscle nuclei with their deeply staining nucleoli were seen arranged circularly about the trichinæ lying in the finely granular, faintly staining, degenerated muscular substance.

Near the infested fibres were found degenerating areas made up of disintegrating bits of muscle fibre, muscle nuclei, small round cells, and polymorphonuclear cells, a great many of whose granules were eosinophilic. These eosinophilic cells were especially prevalent about the bits of degenerating muscle and were certainly as numerous as in the first case.

There was the peculiar granular degeneration of the muscle fibres noted before, and the proliferation of the muscle nuclei in the neighborhood of the parasite.

The trichinæ were young, only slightly curled up and of course non-encapsulated.

In severity, clinically, this case lies midway between the first and second cases, and this position is borne out by the number of parasites found in the muscle excised, by the leucocytosis and by the grade of eosinophilia.

SUMMARY.

To summarize, we have been able to demonstrate:

(1) In a case of acute trichinosis an extensive leucocytosis, with great absolute and relative increase in the number of eosinophilic cells in the blood, associated with a coincident decrease in the quantity of neutrophilic elements.

(2) From the examination of specimens of muscle removed during life, besides the peculiar degenerations of the muscle, a longitudinal

splitting of some of the fibres; a remarkable transverse splitting of others; a great proliferation of nuclei, about many of which vacuoles are seen; and large numbers of polymorphonuclear eosinophilic cells, which are especially prevalent in the more degenerated areas.

(3) In a second case (after death), besides similar changes in the muscle, large numbers of eosinophiles throughout the infested portion.

(4) In two other cases, during life, a great increase of the eosinophilic cells in the blood, with a coincident decrease of the polymorphonuclear neutrophiles, associated with leucocytosis, though of less extent than in the first case.

(5) In pieces of muscle removed in these last two cases changes in most respects similar to those cited in the first case, but of less degree.

(6) The similar character of the nuclei of the eosinophiles and the neutrophiles both in the blood and in the muscle, and the presence in the first case of certain cells which might be regarded as forms transitional between neutrophiles and eosinophiles, suggesting the possibility that the increase in the latter elements may, in these instances, take place in the muscles by direct transition from the neutrophiles.

CONCLUSIONS.

From these observations it is fair to conclude:

1st. That there is a marked increase in the percentage of eosinophilic cells in the blood in trichinosis.

2nd. That this increase may be used as a diagnostic sign in this disease.

3rd. That this disease in its sporadic form is more common than has hitherto been supposed, as shown by the discovery of the three cases above described, within a comparatively short period, at the Johns Hopkins Hospital.

4th. That a systematic examination of the blood should be undertaken in cases with indefinite intestinal, muscular or articular symptoms, in the hope that in some, at least, of the hitherto doubtful cases a diagnosis may be reached.

In conclusion I wish to express to Professor William Osler my sincere appreciation of his kindness in giving me the opportunity of

studying these cases, and to Dr. William Sidney Thayer my hearty thanks for his help during the course of this investigation.

DESCRIPTION OF PLATES XXV–XXVII.

PLATE XXV.

Chart showing graphically the total number and percentages of the various kinds of leucocytes.

PLATE XXVI.

From the blood of Case I, showing a typical field, containing six eosinophiles, with polymorphous nuclei, one polymorphonuclear neutrophile, one large mononuclear leucocyte and many erythrocytes.

PLATE XXVII.

Showing degenerating area in muscle in neighborhood of trichina, demonstrating beginning loss of striation in two fibres, complete loss in a third, and in the rest of the specimen, muscle nuclei, bits of degenerating muscle tissue and many polymorphonuclear eosinophiles. Haidenhain-Biondi triple stain.

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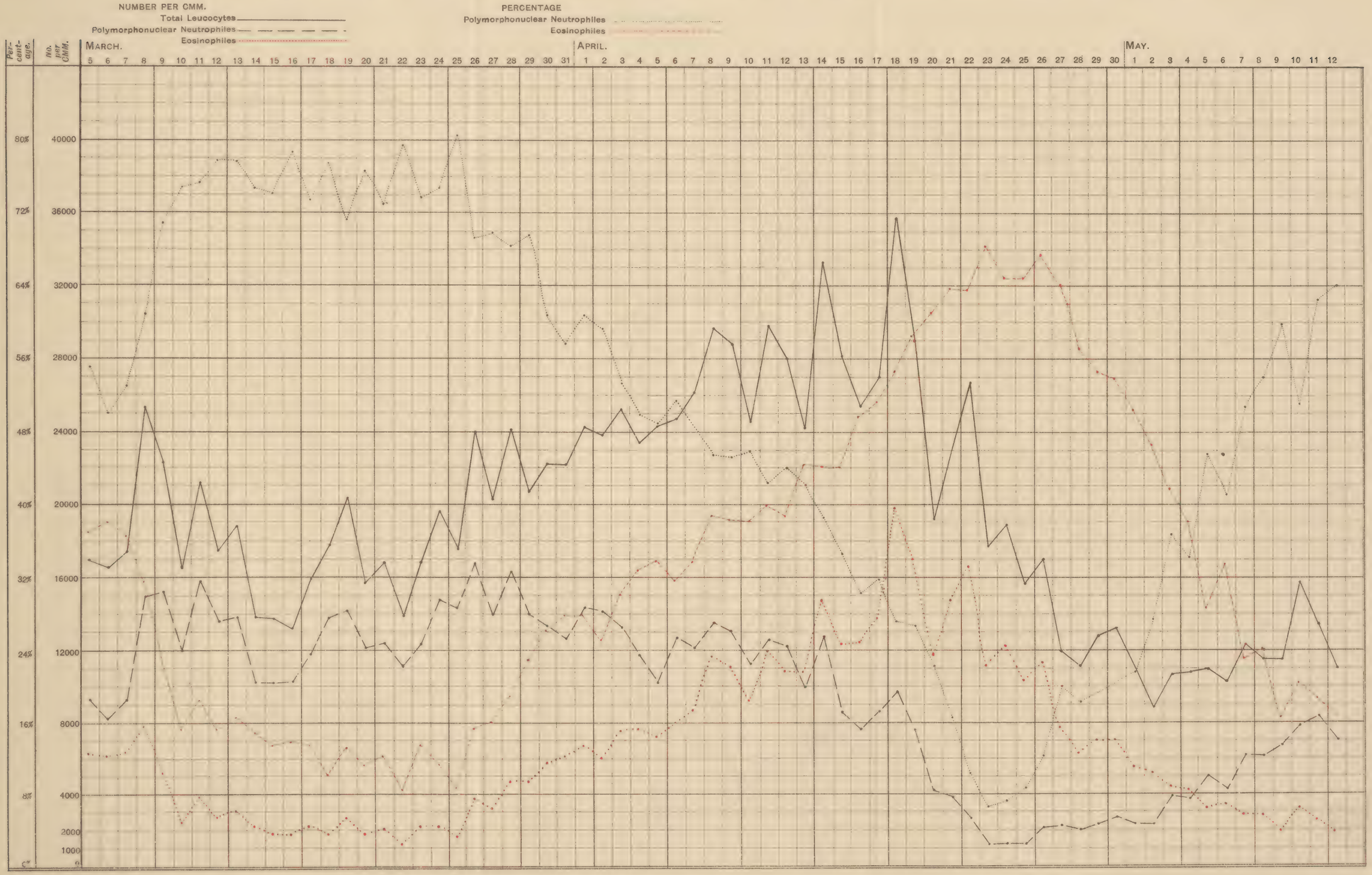
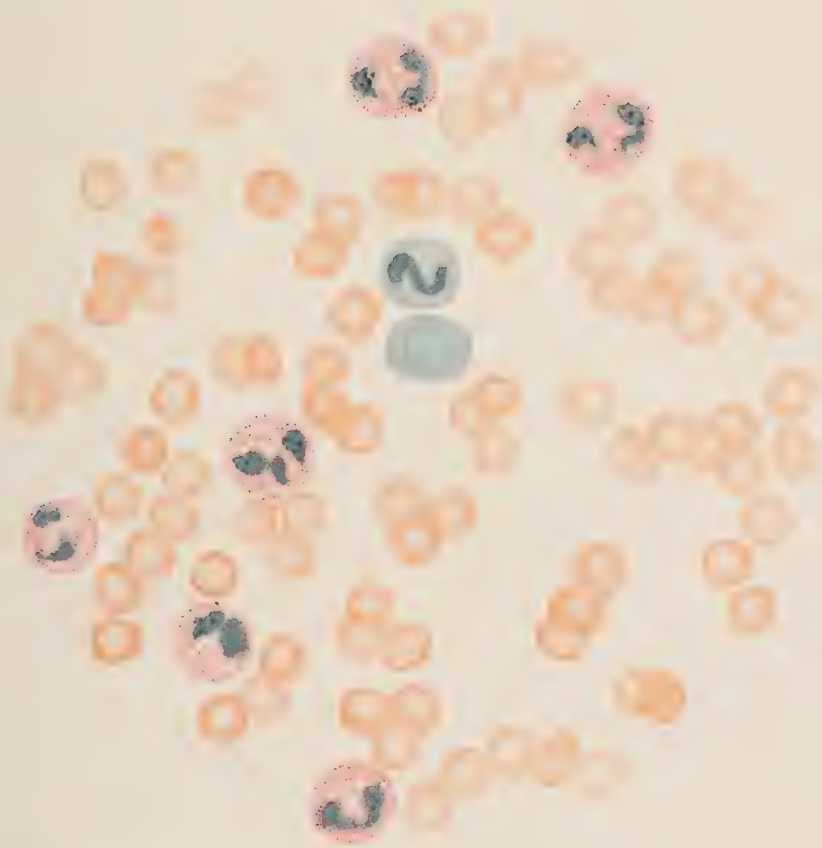
LEUCOCYTIC CHART OF CASE I.

Showing Total Number of Leucocytes, of Polymorphonuclear Neutrophiles and of Eosinophiles, and also the Percentage of Polymorphonuclear Neutrophiles and of Eosinophiles.





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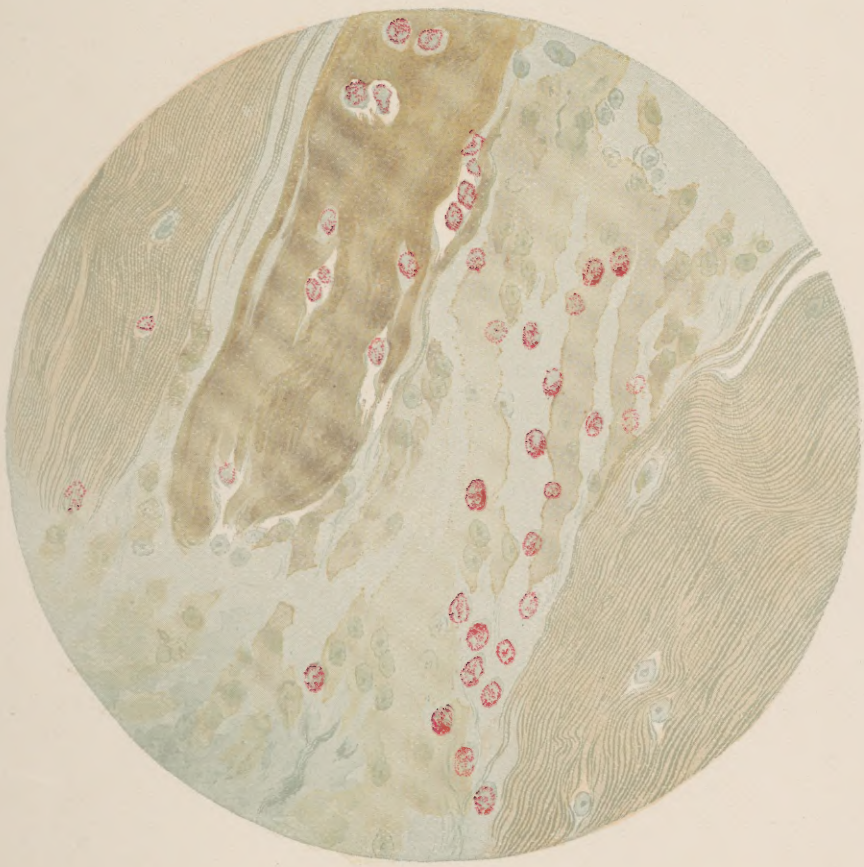

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